Remarks

Claims 1, 3-6 and 8-11 are pending. No amendments have been made.

Section 102 Rejections

The Examiner has maintained the rejection of claims 1, 3-6 and 9-11 under 35 U.S.C. §102(b) as being anticipated by WO 98/12345 ("Politino (A)"). The Examiner continues to allege that Politino (A) teaches a method for producing desacetylcephalosporin C using a cephalosporin esterase for *Rhodosporidium toruloides* (Example 2). This rejection is respectfully traversed.

As noted in Applicants' previous response, Politino (A) describes the cloning and sequencing of *R. toruloides* cephalosporin esterase genomic and cDNA genes. It does not, however, describe the direct fermentation of desacetylcephalosporin C by expression of the cephalosporin esterase gene in *A. chrysogenum*, as in the present invention. The sections of Politino (A) relied on by the Examiner merely show the characterization of the cephalosporin esterase so produced.

Specifically, in Example 2, the esterase enzyme is added to a reaction mixture containing cephalosporin (emphasis added). A by-product of that reaction was desacetyl cephalosporin C, evidencing the efficacy of the recombinantly produced enzyme. This is not relevant, however, to a discussion of the present invention which involves a recombinant fungal organism capable of directly fermenting desacetylcephalosporin C. The Examiner has not provided a reference showing a process for the direct production of desacetylcephalosporin C which comprises culturing a strain of *Acremonium chrysogenum* that contains (1) nucleic acid encoding enzymes for cephalosporin C biosynthesis and (2) a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase, under the stated conditions.

Turning to the Examiner's rejection in detail, the Examiner points to Example 2 in Politino (A) and states that desacetylcephalosporin C is produced by transforming *C. acremonium* (a.k.a. *A. chrysogenum*) with DNA encoding R. esterase. The Examiner goes on to state that *A. chrysogenum* is "producing cephalosporin C and contains nucleic acid encoding enzymes for cephalosporin C biosynthesis and recombinant nucleic acid encoding R. esterase" and concludes that this anticipates the present invention. However, this is not Applicants' invention. Rather, Applicants' invention is a process for the direct production of desacetylcephalosporin C using a single recombinant organism which produces both cephalosporin C and cephalosporin esterase. In Example 2 of Politino (A), the recombinantly produced enzyme is added to cephalosporin (Column 9, line 60) in order to characterize the enzyme. There simply is no direct production of desacetylcephalosporin C using a single organism in the manner set forth in the present invention.

The Examiner points specifically to Claims 26-28 in Politino (A). However, those claims do not set forth the process of the present invention. Applicants point out that cloning of the gene coding for the enzyme is required for heterologous expression of an active enzyme, but it does not necessarily follow that the enzyme will be readily expressed in an active form. In fact, efforts to express this enzyme in an *E. coli* host did not result in an active protein, as describe at pages 37-38 of the present specification. As discovered in the present invention, active expression of the enzyme requires a suitable glycosylation pattern, intron splicing and removal of the N-terminal leader sequence. Therefore, the expression of the esterase enzyme is *A. Chrysogenum* under conditions which allow sufficient expression for the esterase enzyme for the conversion of cephalosporin C to desacetylcephalsoporin, such that the conditions of the present claims are satisfied, are not set forth in Politino (A).

The Examiner is respectfully requested to point out where each and every element of the present claims (as required by Section 102) are set forth in Politino (A), present Claim 1 having the following elements: (1) a process for the direct production of desacetylcephalosporin C which includes; (2) culturing a strain of *Acremonium chrysogenum* containing nucleic acid encoding enzymes for (a) cephalosporin C biosynthesis and (b) a recombinant nucleic acid encoding *Rhodosporidium* cephalosporin esterase (3) under conditions wherein the temperature is about 22°C to about 29°C and the pH is about 5.5 to about 7.5 (4) resulting in the synthesis of cephalosporin C and expression of cephalosporin esterase (5) wherein the cephalosporin C so produced is converted to desacetylcephalosporin C and (6) the chemical breakdown of cephalosporin C to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid is less than 40%.

For the reasons set forth above, Applicants respectfully submit that Politino (A) does not teach or suggest the elements of the claimed invention and is therefore not a proper reference under Section 102.

The Examiner has also maintained the rejection of Claims 1, 3-6 and 9-11 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,869,309 ("Politino (B)"). Politino (B) is the U.S. counterpart of Politino (A) which is a PCT application and contains the same teachings. Accordingly, for the same reasons set forth above, Applicants respectfully submit that Politino (B) does not teach or suggest the element of the claimed invention and is therefore not a proper reference under Section 102.

For these reasons, Applicants respectfully submit that withdrawal of the rejections under Section 102 is appropriate and is respectfully requested.

Section 103 Rejection

The Examiner has maintained the rejection of Claim 8 under 35 U.S.C. §103(a) as being unpatentable over Politino (A) or (B) in view of U.S. Patent No. 4,533,632 ("Smith"). The Examiner alleges that Smith teaches a process for the preparation of desacetylcephalosporin C by fermenting *Acremonium chrysogenum* in the presence of esterase from *Rhodosporidium toruloides.* The process of fermentation is carried out at 15º-45º C and pH 4-9. The Examiner alleges that it would have been obvious at the time of the present invention to use *Acremonium chrysogenum* transformed with a DNA encoding *Rhodosporidium toruloides* esterase in the production of desacetylcephalosporin C.

The Examiner has only made conclusory statements without providing the requisite motivation necessary for a proper rejection under Section 103. The Examiner states that the motivation is provided at pages 6-7 of the Final Office Action, but Applicants again submit that these are merely conclusory statements. The Examiner does not point to specific instances within the references where the motivation is provided. In any event, Applicants submit that the point is moot as the deficiencies of Politino (A) and (B) noted above cannot, of course, be remedied by the teachings of Smith.

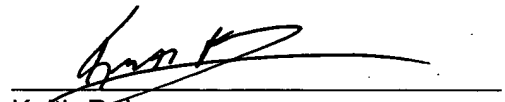
Accordingly, Applicants respectfully submit that withdrawal of the rejection under Section 103 is appropriate and is respectfully requested.

Conclusion

In view of the amendments and remarks above, Applicants submit that the claims are in condition for allowance and favorable action is therefore respectfully requested.

Please direct any questions regarding this reply to the undersigned attorney.

Respectfully submitted,



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